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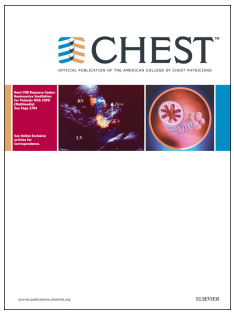

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Collateral ventilation measurement using Chartis: procedural sedation versus general anesthesia

Jorrit B.A. Welling MD[1,2], Karin Klooster PhD[1,2], Jorine E. Hartman PhD[1,2], Huib A.M. Kerstjens MD PhD[1,2], Ina Franz MD[3], Michel M.R.F. Struys MD PhD[3], Anthony R. Absalom MD PhD[3], Dirk-Jan Slebos MD PhD[1,2] and Clemens R.M. Barends MD[3]

Affiliation:

1. University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases, Groningen, the Netherlands.

2. Groningen Research Institute for Asthma and COPD, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

3. University of Groningen, University Medical Center Groningen, Department of Anaesthesiology, Groningen, the Netherlands.

Corresponding author: Jorrit B.A. Welling, MD. Department of Pulmonary Diseases AA11, University Medical Center Groningen, P.O.Box 30001, 9700RB Groningen, the Netherlands. E-mail: j.b.a.welling@umcg.nl. Telephone: +3150-3610280

Key words: endobronchial valve treatment, collateral ventilation, Chartis measurement, procedural sedation, general anesthesia

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Abbreviations list:

BIS	Bispectral index
BLVR	Bronchoscopic lung volume reduction
Ce	Effect-site concentration
CV	Collateral ventilation
EBV	Endobronchial valve
FEV_1	Forced expiratory volume in 1 second
GA	General anesthesia
HRCT	High resolution computed tomography
PS	Procedural sedation
RV	Residual volume
TCI	Target controlled infusion
TLC	Total lung capacity

Abstract:

Background: Absence of interlobar collateral ventilation is key to successful endobronchial valve treatment in patients with severe emphysema and can be functionally assessed using the Chartis® measurement. Chartis has been validated during spontaneous breathing, undergoing procedural sedation (PS), but can also be performed under general anesthesia (GA). Performing Chartis under PS is often challenging because of coughing, mucus secretion and difficulties in maintaining an adequate level of sedation. The study objective was to investigate whether there is a difference in Chartis measurement outcomes between PS and GA.

Methods: In this prospective study patients underwent Chartis measurements under both PS and GA. Study outcomes were Chartis measurement duration, number of measurements, feasibility and success rate.

Results: We included 30 patients with severe emphysema (mean age 62 years and median FEV_1 29% of pred.). Chartis measurement duration was significantly longer under PS than under GA (mean 20.3±4.2 minutes versus 15.1±4.4, P<0.001). There was no difference in the number of measurements performed (median 2 (range 1-3) for PS versus 1 (1-3) for GA, P=1.00). Chartis measurement was more feasible during GA (median sum of all feasibility scores: 12 (range 6-26) for PS versus 7 (5-13) for GA, P<0.001), with no statistical difference in success rate: 77% of cases for PS versus 97% under GA, P=0.07.

Conclusion: This study shows that Chartis measurement under general anesthesia is faster and more feasible to perform compared to procedural sedation, without affecting measurement outcomes.

Registration: Clinicaltrials.gov; No. NCT03205826; URL: www.clinicaltrials.gov

Introduction:

Bronchoscopic lung volume reduction (BLVR) using endobronchial valves (EBV) is an effective and safe treatment for selected patients with severe emphysema[1–4]. To achieve EBV treatment benefit, interlobar collateral ventilation (CV) must be absent, as the presence of CV prevents the desired atelectasis of the target lobe[5]. The presence of CV can be assessed using indirect measurement techniques such as quantitative computed tomography fissure analysis and hyperpolarized gas magnetic resonance imaging or direct techniques such as collateral flow measurement during bronchoscopic assessment with the Chartis System® (Pulmonx Inc., Redwood City, CA, USA)[6,7]. The Chartis system consists of a catheter which is designed to be advanced through the working channel of a flexible bronchoscope and uses an inflatable balloon at the tip of the catheter to selectively occlude the entrance of a lung lobe (see figure 1). The system measures flow from the occluded lobe and calculates the resistance to airflow through collateral channels and quantifies the amount of CV within a specific lobe[8].

In our BLVR treatment expert center, all patients scheduled for EBV treatment undergo a Chartis measurement to determine CV status. Chartis measurement was originally validated in patients breathing spontaneously undergoing procedural sedation (PS)[9]. However, performing a Chartis measurement under PS can be very challenging because of problems with catheter placement caused by coughing reflexes of the patient, mucus secretions that can occlude the catheter, swelling of the airway mucosa causing challenging measurements and difficulties in maintaining a sufficient level of sedation. Although in several recent

EBV trials as well as in our ongoing regular treatment program BREATH-NL (NCT02815683) we have performed Chartis measurement under general anesthesia (GA), the measurement has not yet been validated under GA[2–4]. We recently published a retrospective analysis on this topic, suggesting advantages of Chartis measurement under GA with shorter procedure times and fewer measurements necessary, without a difference in target lobe volume reduction after EBV treatment[10]. The objective of this study was to prospectively compare Chartis measurement under PS versus GA. We hypothesized that Chartis measurement under GA would result in faster procedures with higher physician assessed feasibility and with similar diagnostic outcome.

Methods:

Study design and participants:

We performed a single center prospective study in which we included patients with severe emphysema (NCT03205826), who met the inclusion criteria for EBV treatment[5]. For safety reasons, patients that met the following criteria were excluded from participation: forced expiratory volume in one second (FEV_1)<20% of predicted, residual volume/total lung capacity (RV/TLC) ratio >70%, pCO2>6.5 kPa at baseline at room air, right ventricular systolic pressure>40mmHg on echocardiogram, 6 minute walking distance <200 meter, known intolerance to lidocaine or any medical reason that warranted a short procedure.

The study was approved by the University Medical Center Groningen medical ethics committee (NL62374.042.17) and all patients provided written informed consent.

Procedure:

CV status was evaluated in all patients using Chartis measurement under PS, followed by Chartis measurement under GA in the same procedure. The same lobes were assessed under PS and under GA. In all patients the measurements were performed in the target lobe for EBV treatment and when indicated the measurements were also performed in the ipsilateral or secondary target lobes. Chartis measurement was terminated when either absence of collateral ventilation was confirmed by an airway flow gradually approaching zero (with airway resistance > 10cm H_2O x ml/s for PS) in combination with immediate return of airway flow upon release of the balloon catheter (ruling out catheter obstruction), or when the presence of collateral ventilation was confirmed with the observation of a continuous, non-decreasing, expiratory airway flow during >6 minutes or totaling > 1 liter[11,12]. All Chartis measurements were performed by one interventional pulmonologist, who had previous experience with this measurement under PS and GA (DJS).

Anesthetic management:

Anesthetic management consisted of two phases: PS and GA. Patient monitoring during both phases consisted of 3-lead ECG, SpO_2, non-invasive blood pressure monitoring, end-tidal CO_2 measurement and electroencephalography based depth of sedation monitoring using a BIS monitor (BIS VISTA®, Medtronic, Dublin, Ireland).

PS was induced using infusions of propofol and remifentanil. Propofol (20mg/ml) was administered by effect-site (Ce) targeted-controlled infusion (TCI) using the Schnider model with a starting target Ce concentration of 1 µg/ml[13]. Remifentanil (50 µg/ml) was administered by effect-site (Ce) TCI using the Minto model

starting at an initial target Ce of 1.0 ng/ml[14]. Sedation depth was controlled primarily by adjusting the propofol target Ce concentration while the target remifentanil Ce was reduced on indication but rarely increased above 1.0 ng/ml. Lidocaine 10mg/ml was applied topically to the larynx by the interventional pulmonologist. Sedation was maintained in the time period between the PS phase and the GA phase.

In order to pre-oxygenate the lungs adequately for the induction of GA, patients were administered 100% O_2 through a tight fitting face mask while still under PS. After pre-oxygenation Ce-propofol and Ce-remifentanil were increased to induce GA, rocuronium-bromide 0.3-0.6 mg/kg was administered and endotracheal intubation was performed by the attending anesthesiologist using a cuffed Shiley™ Hi-contour Oral/Nasal Tracheal Tube (Covidien™, Mansfield, USA) with an internal diameter of 9mm. Thereafter GA was maintained with TCI-propofol and remifentanil and the patients lungs were mechanically ventilated. The primary ventilator settings were: volume controlled ventilation mode, fraction of inspired oxygen 50%, positive end-expiratory pressure 3cm H_20, tidal volumes of 4 to 6ml/kg, respiratory rate 10/min and an inspiratory:expiratory ratio of 1:3 to 1:4. The adjustment of these settings, to ensure patient-safety, was left to the discretion of the attending anesthesiologist.

Outcome measures:

The primary outcome measure was the difference in duration of Chartis measurement between the sedation and GA. Secondary outcome measures were the time until the patient was sufficiently sedated to undergo Chartis measurement, success rate of Chartis measurement, number of measurements performed and qualitative feasibility assessment between the two anesthesia

methods. The duration of the Chartis measurement was defined as the time between the start of the applicable anesthesia phase (PS or GA) and the withdrawal of the Chartis catheter from the bronchoscope after Chartis measurement. Start of PS phase was defined as the start of propofol or remifentanil. Start of the GA phase was defined as the increase of propofol and remifentanil dosage for induction of GA. The time until the patient was sufficiently sedated to undergo Chartis was defined as the time between start of the PS or GA phases and the first advancement of the Chartis catheter through the bronchoscope. Measurements were considered successful when collateral ventilation status was classified as either positive or negative. A single measurement was defined as the data collected between initiation and termination of the measurement on the Chartis console. Chartis measurement was only performed once per lobe per patient, unless a measurement was considered unsuccessful. Feasibility of the measurement was scored for both PS as well as GA by the physician performing the measurement, using a 1-10 visual analog scale, with lower scores indicating better feasibility. Five sub-scores were scored: presence of mucus, amount of coughing, degree of airway collapse, need for breathing instruction (for PS only) and measurement feasibility. We calculated the sum of all sub-scores to assess overall feasibility.

Statistical analysis:

The sample size calculation was based on a previous study from our group, in which the average time of Chartis measurement was 1283±720 seconds under PS and 818±477 seconds under GA[10]. A paired samples t-test was performed and to reach a power of 80% with an alpha level of 0.05 and considering a 10% drop-out rate, a total of 30 patients were required.

Differences in duration, time until the patient was sufficiently sedated to undergo Chartis, number of measurements and feasibility score outcomes of the Chartis measurement between PS and GA were analysed using a paired samples t-test in case of normal distribution or a Wilcoxon signed rank test in case of non-normal distribution of data. The difference in success rate between the anesthesia methods was analysed using McNemar's test. Confidence intervals for non-normally distributed data were determined using Hodges Lehmann Estimator. Statistical analyses were performed using SPSS (IBM, New York, NY, USA). P-values<0.05 were considered statistically significant.

Results:

In total, 31 patients signed informed consent, of which in 30 patients Chartis measurements were performed between April 2018 and January 2019. One patient was excluded from further analysis because severe bronchitis was observed during bronchoscopy, leading to ineligibility for EBV treatment and therefore no Chartis measurement was performed. The remaining thirty patients were included in the final analysis (23% male, mean age 63±6 years and median FEV_1 29% (range 21-56) of predicted). Baseline characteristics can be found in table 1. All patients completed the study without unexpected anesthesia related complications or unexpected procedure related complications.

A total of 48 Chartis measurements were performed under PS of which 19 were classified as CV negative and 10 were classified as CV positive. During 7 measurements we encountered a no flow state and 12 measurements were classified as unknown CV status. Forty-eight measurements were performed under GA of which 23 were classified as CV negative and 13 were classified as CV

positive. During 10 measurements we encountered a no flow state and 2 measurements were classified as unknown CV status.

Chartis measurement took significantly longer under PS than under GA. In addition, with the patient under PS, it took significantly longer before the patient was sufficiently sedated to undergo Chartis compared to GA. No significant difference in the number of measurements performed was observed. The success rate of Chartis measurement was higher under GA compared to PS, however not statistically significant. Chartis outcomes are provided in table 2.

Discrepancies in CV status outcome between PS and GA were encountered in 4 measurements. Two measurements that were classified as CV positive under PS were, when measured in the same lobe of the same patient, classified as CV negative during GA, while two other measurements were classified CV negative under PS and CV positive under GA. Out of these 4 patients, 3 underwent EBV treatment and 1 patient was not treated based on a significant contribution of the occluded target lobe to the overall gas exchange of the patient. In one patient who was classified as CV positive under PS and as CV negative under GA, full lobar atelectasis was observed on high resolution computed tomography scan (HRCT) 6 weeks after EBV treatment. In two patients, who were classified as CV negative under PS and as CV positive under GA, treatment did not result in lobar atelectasis on HRCT at 6 weeks follow-up.

Chartis measurements were more feasible under GA compared to PS. During PS, mucus score, coughing score and measurement feasibility were significantly worse compared to GA, while airway collapse did not differ between both methods (table 2).

There was no difference in median Ce propofol during the start of Chartis measurement under PS versus GA. The median Ce remifentanil during the start of Chartis measurement was significantly lower during PS than during GA. The median BIS score at the time of start Chartis measurement was significantly higher during PS compared to GA. All patients were mechanically ventilated during the GA phase. The median tidal volume was 5ml/kg (3-7) and the median plateau pressure observed was 18 cm H_20 (13-38). During PS, a mean of 294 ±55mg lidocaine was administered topically to the patients.

Discussion:

This first prospective study comparing Chartis measurement of CV under PS versus GA showed that Chartis measurement took significantly longer and was less feasible under PS compared to this measurement under GA. The performance of Chartis measurement was less feasible under PS, with more mucus and coughing problems. No statistical differences were found in the number of measurements or the measurement success rate.

Chartis measurement is an important tool used to assess interlobar CV status and achieve EBV treatment success, and should ideally be performed in circumstances that allow for fast and effective measurement, preferably in the same session in which the EBV placement is performed[5].

The differences in duration and feasibility between PS and GA that we found are likely to be caused by more mucus production, causing catheter obstruction, or coughing resulting in problems with catheter positioning, as well as maintaining adequate sedation levels in the PS group, all causing more difficult measurement and interpretation of Chartis results.

The results of this study are in line with a retrospective analysis performed by our group in which longer and more frequent measurements under PS were observed, without a difference in target lobe volume reduction after EBV treatment[10]. The nominal success rate of Chartis measurement in this study was higher for GA, but this difference was not statistically significant.

In addition, and supportive of our findings, a recently published retrospective analysis by Thiruvenkatarajan *et al.* comparing PS and GA suggests better interventional conditions, patient comfort and reduced anesthetic time under GA[15].

No direct unexpected anesthesia related complications or direct unexpected procedure related complications were observed in our study. Thiruvenkatarajan et al. describe occurrence of mild hypotension periods during EBV treatment under GA, in line with expected blood pressure decline after induction of GA and responding to vasopressor bolusses. One case of severe hypotension in the same study was observed which was ascribed to possible anaphylaxis and led to procedure termination[15]. Post-treatment expected complications were not registered for our study. In the recently published LIBERATE trial, post EBV treatment complications were compared between procedures performed under PS versus GA: chest pain occurred in 40% of patients under PS versus 18% under GA, pneumothorax occurred in 24% of patients under PS versus 33% under GA and COPD exacerbations were observed in 22% of patients after PS versus 18% under GA, however no statistical testing was performed to compare the complication rates between the anesthesia methods. In the same trial, no difference in FEV_1 outcome after EBV treatment between the two anesthesia methods was found[4].

Next to the above mentioned disadvantages, performing Chartis under PS also has potential advantages over GA: lower dosages of medication are necessary and no intubation and mechanical ventilation is required. Even though the performance of Chartis measurement under GA is more resource intensive, invasive for the patient and sometimes unavailable in BLVR centers, the use of GA for Chartis measurement is advocated by an expert panel on BLVR[5].

A theoretical argument against the performance of Chartis under GA is that the use of positive pressure ventilation might open CV channels, which would not be open under spontaneous breathing circumstances, leading to a false positive CV outcome. In the current study we did not observe any relevant differences in CV status outcomes between PS and GA. This observation is further supported by our previously published retrospective analysis in which no difference in target lobe volume reduction outcome between the two methods was seen after EBV treatment[10].

Because patients in this study received PS before conversion to GA, the time needed to induce GA could have hypothetically been reduced and led to underestimation of the time before the patient was sufficiently sedated to undergo Chartis measurement. With the TCI-technique used in our institution, however, the time needed to increase remifentanil from PS to GA levels using target-controlled infusion is approximately 80 seconds while the time needed to achieve GA levels of remifentanil when starting from 0 is approximately 90 seconds. In other words, the sedation Ce's of propofol and remifentanil have not led to a significant reduction of the time needed to induce GA while in addition during the induction of GA, the anesthesiologist had to wait around 3 to 4 minutes for the neuromuscular blockade needed for tracheal intubation to take

effect. Finally, all feasibility outcomes were scored by only one physician, which might lead to an observation bias. Furthermore, we only assessed physician feasibility, while ideally the experience of the patients should be taken in consideration as well. Unfortunately this is challenging to investigate as procedure related amnesia occurrence will lead to recall bias.

A strength of our study is that all Chartis measurements were performed by one interventional pulmonologist with experience with Chartis under both anesthesia techniques in one specialized treatment center, which increased standardization. In addition, all patients received both anesthesia techniques in a standardized fashion with medication dosage models and fixed ventilator settings. In our opinion, the fact that all patients received both PS as well as GA is a strength of our study. Ideally, the order in which patients undergo PS or GA first should be randomized, however we considered this approach unfeasible because of practical limitations.

In conclusion, we suggest performing Chartis measurement under general anesthesia because of higher feasibility and shorter procedure times compared to procedural sedation, without losing diagnostic power. The results from this study might result in more efficient and feasible Chartis measurement in future endobronchial valve treatment.

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Guarantor statement: J.B.A.W takes responsibility for the content of the manuscript, including data and analysis.

Author contributions: J.B.A.W., K.K., J.E.H., D.J.S. and C.R.M.B undertook conception and design. D.J.S. and K.K. performed all Chartis measurements and treatments. J.B.A.W., K.K., J.E.H., I.F., D.J.S. and C.R.M.B acquired data. J.B.A.W., J.E.H., D.J.S. and C.R.M.B. performed analysis and interpretation. All authors have read, improved and approved the final manuscript.

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2018;18(1):206.

Tables:

Table 1: Patient characteristics

Characteristics	
n	30
Female/Male (%)	77/23
Age (years)	62.8±5.7
BMI (kg/m^2)	23.9±3.9
Pack-years (years)	49 (15-126)
FEV_1%predicted (%)	29 (21-56)
RV%predicted (%)	227 (181-300)
RV/TLC (ratio)	0.6 (0.6-0.8)
pC02 in arterial blood gas (kPa)	5.3±0.6
6MWD (meter)	369 (120-477)
SGRQ total score (units)	54.7±11.0

Data are presented as mean ± standard deviation in case of normal distribution of data and as median(range) in case of non-normal distribution. BMI: Body mass index; FEV_1: forced expiratory volume in one second; RV: Residual volume; TLC: Total lung capacity; 6MWD: 6-minute walking distance; SGRQ: St. George's Respiratory Questionnaire

Table 2: Chartis measurement outcomes under procedural sedation and general anesthesia

	Procedural sedation	General Anesthesia	Difference	P-Value
Measurement				
Duration of total Chartis procedure per patient (minutes)	20.3±4.2	15.1±4.4	5.2 [3.4-7.1]	P<0.001
Time until patient was sufficiently sedated to undergo Chartis measurement (minutes)	12.5±3.0	7.6±1.8	4.9 [3.7-6.1]	P<0.001
Number of measurements per patient (number)	2 (1-3)	1 (1-3)	0 [0-0]	P=1.00
Success rate (%)	77%	97%	NA	P=0.07
Feasibility				
Sum of feasibility scores (score)	12 (6-26)	7 (5-13)	6 [4-8]	P<0.001
Mucus (score)	4 (2-8)	3 (1-5)	2 [1-3]	P<0.001
Coughing (score)	4 (1-8)	1 (1-1)	3 [2-4]	P<0.001
Airway collapse (score)	2 (1-8)	1 (1-4)	1 [0-1]	P=0.06
Feasibility (score)	3 (1-7)	2 (1-4)	1 [1-2]	P<0.01
Breathing instruction during procedural sedation (score)	2 (1-10)	NA	NA	NA

Anesthesia				
Propofol effect site concentration at time of start Chartis measurement (µg/ml)	3 (1-5)	3 (2-5)	-0.4 [-1-0.1]	P=0.09
Remifentanil effect site concentration at time of start Chartis measurement (ng/ml)	1 (1-2)	4 (2-5)	-3 [-3--3]	P<0.001
BIS score at time of start Chartis measurement (score)	76(46-88)	39 (24-64)	35[29-38]	P<0.001

Data are presented as mean ± standard deviation in case of normal distribution of data and as median (range) in case of non-normal distribution. The differences between the anesthesia methods are presented as mean or median [95% confidence interval]. Confidence intervals for non-normally distributed data were determined using Hodges Lehmann Estimator. Differences in outcomes between procedural sedation and general anesthesia were analyzed with a paired samples t-test in case of normal distribution of data or a Wilcoxon signed rank test in case of non-normal distribution of data. The difference in success rate of the measurements was analysed using a McNemar's test. NA: Not applicable. BIS: Bispectral index. Mucus, coughing, airway collapse, feasibility and breathing instruction were scored on a 0 to 10 scale, with a score of 0 indicating, no mucus, no coughing, no airway collapse, very feasible measurement and no breathing instruction, and a score of 10 indicating, large amounts of mucus, severe coughing, severe airway collapse, very unfeasible measurement and continuous breathing instruction necessary.

Figure legends:

Figure 1: Chartis measurement system


Review
Ventilator
RUL - 1
Assess Time
02:04
VOL (mL)
94
Assess Date
28/02/2013
11:47:20 AM
RUL - 1 of 1
Accepted
pulmonX